IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Philipp Hadwiger et al.
Serial No:	10/543,048
Confirmation No:	3878
Filed:	January 26, 2006
For:	LIPOPHILIC DERIVATIVES OF DOUBLE-STRANDED RIBONUCLEIC ACID
Examiner:	Chong, Kimberly
Art Unit:	1635

APPEAL BRIEF PURSUANT TO 37 C.F.R. § 41.37

Commissioner for Patents
Mail Stop Appeal Brief - Patents
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Sir:

As set forth in the Notice of Appeal filed April 11, 2010, Appellants hereby appeal the examiner's final rejection of claims 86, 94-98, 100-102, 110-111, and 114-119 of the above-identified application.

Appellants respectfully request that the Board of Patent Appeals and Interferences reverse the rejection of these claims.

I. REAL PARTY IN INTEREST

The real party in interest is Alnylam Pharmaceuticals, the assignee of U.S. Patent Application Serial No. 10/543,048. The assignment from the inventors to Alnylam Europe AG was recorded in the U.S. Patent and Trademark Office on Reel/Frame 017216/0009 on January 26, 2006, and the assignment from Alnylam Europe AG to Alnylam Pharmaceuticals was recorded in the U.S. Patent and Trademark Office on Reel/Frame 023120/0064 on August 19, 2009.

II. RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences pertaining to the above-identified application.

III. STATUS OF CLAIMS

Claims 86, 94-98, 100-102, 110-111, and 114-119 are currently pending. Claims 1-85, 87-93, 99, 103-109, and 112-113 have been cancelled.

This represents the second time Applicants have taken this application to appeal. On March 23, 2010, a Notice of Appeal was filed on these same claims, followed by the filing of an Appeal Brief on May 21, 2010. The examiner reopened prosecution and issued a new Office Action. The new Office Action removed two of the three secondary references and added three additional secondary references.

Claims 86, 94-98, 100-102, 110-111, and 114-119 stand rejected in the Office Action mailed January 18, 2011 under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent Application Publication No. 2003/0139363 to Kay et al. ("Kay") in view of U.S. Patent Application Publication No. 2003/0143732 to Fosnaugh et al. ("Fosnaugh"), the Manoharan article entitled, "Oligonucleotide conjugates as potential antisense drugs with improved uptake, biodistribution, targeted delivery, and mechanism of action" *Antisense & Nucleic Acid Drug Development*, 2002, 12:103-128 ("Manoharan"), the Mackellar et al. article entitled, "Synthesis and physical properties of anti-HIV antisense oligonucleotides bearing terminal lipophilic groups" *Nucleic acid Research*, 1992, 20(13): 3411-3417 ("Mackellar"), and evidenced by Virta

article entitled "Solid-supported synthesis of oligomeric bioconjugates" *Tetrahedron*, 2003, 59:5137-5174 ("Virta").

The decision of the examiner rejecting claims 86, 94-98, 100-102, 110-111, and 114-119 is hereby appealed. Claims 86, 94-98, 100-102, 110-111, and 114-119 are set forth in the attached Claims Appendix.

IV. STATUS OF AMENDMENTS

There are no amendments pending. All previous amendments and new claims were entered by the examiner.

V. SUMMARY OF CLAIMED SUBJECT MATTER

Claim 86 is directed to a double-stranded ribonucleic acid (dsRNA) comprising a complementary RNA strand, a sense RNA strand and only one lipophilic group having a $\log K_{ow}$ exceeding 1. The complementary RNA strand has a nucleotide sequence which is complementary to a target RNA. The target RNA is a mRNA transcript of a target gene or of a (+) strand RNA virus. The lipophilic group is covalently attached to a 5'-end of the complementary RNA strand and a linkage between the lipophilic group and the 5'-end of the complementary RNA strand comprises a phosphodiester group. Support for claim 1 may be found in original claims 1-4 and 24, and pages 4-5 of the specification.

Claim 94 is directed to the dsRNA of claim 86, wherein the lipophilic group is a steroid or a branched aliphatic hydrocarbon, or a combination thereof. Support for this claim may be found in the specification on page 7, lines 12-15 and page 14, line 27 to page 15, line 22.

Claim 95 is directed to the dsRNA of claim 94, wherein the lipophilic group is a sterol. Support for this claim may be found in the specification on page 15, lines 15-22.

Claim 96 is directed to the dsRNA of claim 95, wherein the sterol is cholesterol or a cholesterol derivative. Support for this claim may be found in the specification on page 15, lines 15-22.

Claim 97 is directed to the dsRNA of claim 96, wherein the lipophilic group is cholesteryl (6-hydroxyhexyl) carbamate or 12-hydroxydodecanoic acid bisdecylamide. Support for this claim may be found in the specification on page 14, line 27 to page 16, line 22.

Claim 98 is directed to the dsRNA of claim 86, wherein the lipophilic group is selected from the group consisting of an aromatic, aliphatic or alicyclic moiety, or a combination thereof. Support for this claim may be found in the specification on page 14, line 27 to page 17, line 1.

Claim 100 is directed to the dsRNA of claim 86, wherein the lipophilic group has a $\log K_{ow}$ exceeding 1.5. Support for this claim may be found in the specification on page 13, lines 3-21.

Claim 101 is directed to the dsRNA of claim 86, wherein the lipophilic group has a $\log K_{ow}$ exceeding 2. Support for this claim may be found in the specification on page 13, lines 3-21.

Claim 102 is directed to the dsRNA of claim 86, wherein the lipophilic group has a $\log K_{ow}$ exceeding 3. Support for this claim may be found in the specification on page 13, lines 3-21.

Claim 110 is directed to the dsRNA of claim 86, wherein the complementary RNA strand comprises a 3'-end and a 5'-end, and wherein the 3'-end has a nucleotide overhang of 1 to 4 nucleotides. Support for this claim may be found in the specification on page 16, lines 16-29.

Claim 111 is directed to the dsRNA of claim 86, wherein the complementary RNA strand comprises a 3'-end and a 5'-end, and wherein the 3'-end has a nucleotide overhang of 1 or 2 nucleotides. Support for this claim may be found in the specification on page 16, lines 16-29.

Claim 114 is directed to the dsRNA of claim 86, wherein the dsRNA is between 16 and 30 nucleotides in length. Support for this claim may be found in the specification on page 16, lines 9-15.

Claim 115 is directed to the dsRNA of claim 86, wherein the dsRNA is between 16 and 25 nucleotides in length. Support for this claim may be found in the specification on page 16, lines 9-15.

Claim 116 is directed to the dsRNA of claim 86, wherein the dsRNA is between 20 and 25 nucleotides in length. Support for this claim may be found in the specification on page 16, lines 9-15.

Claim 117 is directed to the dsRNA of claim 86, wherein the target RNA is expressed in a cell selected from the group consisting of a hepatocyte, a pancreatic cell, a uterine cell, a cell of

a cervix, and a cell of a urinary bladder. Support for this claim may be found in the specification on page 9, lines 19-25, and original claim 66.

Claim 118 is directed to the dsRNA of claim 86, wherein the (+) strand RNA virus is a Hepatitis C Virus (HCV). Support for this claim may be found in the specification on page 9, lines 19-25, and original claim 67.

Claim 119 is directed to the dsRNA of claim 86, wherein the target RNA is at least a portion of a 3'-untranslated region (3'-UTR) of a Hepatitis C Virus (HCV). Support for this claim may be found in the specification on page 9, lines 19-25 and original claim 68.

VI. GROUNDS OF REJECTION TO BE REVIEWED UPON APPEAL

Appellants respectfully request that the Board reverse the rejection of claims 86, 100-102, 110-111, and 114-119 under 35 U.S.C. § 103(a) as being unpatentable over Kay in view of Fosnaugh, Manoharan, MacKellar, and Virta.

VII. ARGUMENT

Claim 86 recites a double-stranded ribonucleic acid (dsRNA) comprising a complementary RNA strand, a sense RNA strand and only one lipophilic group having a $\log K_{ow}$ exceeding 1. The complementary RNA strand has a nucleotide sequence which is complementary to a target RNA, and wherein the target RNA is an mRNA transcript of a target gene or of a (+) strand RNA virus. The lipophilic group is covalently attached to a 5'-end of the complementary RNA strand and a linkage between the lipophilic group and the 5'-end of the complementary RNA strand comprises a phosphodiester group.

Kay, according to the examiner teaches dsRNA that efficiently inhibit viral gene expression, and the use dsRNA capable of inhibiting the expression of a Hepatitic C Virus to target hepatocyte cells. See Office Action mailed July 30, 2010, page 8. Kay does not teach a lipophilic group linked at the 5' end of the antisense strand of a dsRNA with a phosphodiester group, as required by the pending claims. To cure these deficiencies, the examiner relies heavily on Fosnaugh. Specifically, the examiner cites Fosnaugh as teaching a dsRNA that comprises a conjugate covalently attached to the dsRNA, with broad language suggesting that the conjugate

may be attached to either end of either strand. The examiner also relies on Fosnaugh for teaching that the conjugate can be linked with biodegradable linkers and phosphodiester linkages. See Office Action mailed March 19, 2009, page 4. Manoharan, Mackellar and Virta are cited, according to the examiner, to provide the motivation for attaching a lipophilic group to the 5' end of the antisense strand of a dsRNA.

The examiner, however, has not produced a single reference showing a dsRNA linked to a lipophilic conjugate (having a $\log K_{ow}$ exceeding 1) <u>via a phosphodiester group</u> through the 5' end of the antisense strand, where (a) the dsRNA was able to reduce gene expression, and (b) the dsRNA did not contain a free hydroxyl group on the 5' end of the antisense strand. It was not until this invention that the inventors recognized that a highly lipophilic group can be conjugated on the 5' end of the antisense strand in a manner that improved RNA interference activity and improved the biological activity of the dsRNA.

The examiner cites Fosnaugh as disclosing conjugation through the 5' end of the antisense strand. However, Appellants are not disputing that one skilled in art would not have contemplated the possibility of conjugating at the 5' end of the antisense strand. Fosnaugh was simply stating that the *specific conjugates* disclosed in this reference (not the conjugates recited in Appellants' claimed invention) can be attached at one of the ends of the strand.

Fosnaugh is also cited for the proposition that the conjugate can be attached through known biodegradable linkers, including phosphodiester linkages. But again, the focus of Fosnaugh lies in the specific conjugates of Fosnaugh with those particular linkers. Fosnaugh does not suggest any special function or relationship that can be applied to other conjugates and linkers.

When taking into account the full disclosure of Fosnaugh, it becomes clear that there are numerous possibilities disclosed within the reference (or generally known by one of ordinary skill in the art) for choosing different linkages, different conjugates, and different ways to attach the conjugate to the dsRNA. However, there is no direction given why one skilled in the art would pursue the path identified by the examiner rather than the many other disclosed alternatives. Just because Fosnaugh states that the particular conjugates disclosed in that reference may be placed on any position in the dsRNA does not mean that the reference teaches that *any conjugate* can be placed in *any position* in the strand *with a reasonable expectation of*

success. See MPEP § 2143.02 (a reasonable expectation of success is required; at least some degree of predictability is required to show obviousness).

Variation in even one of the variables when modifying the references can lead to any number of different compounds and not to those of the claimed invention. The examiner has not presented any rationale for showing how one of ordinary skill would navigate through each possibility disclosed by Fosnaugh, incorporating the alternatives that would work while disregarding those that would not work. Fosnaugh itself certainly provides no guidance on why certain positions of the dsRNA should be used for attachment or why certain linkages should be utilized.

The rejection set forth by the examiner follows a similar obviousness analysis that was rejected by the Federal Circuit in *Ortho-McNeil Pharm., Inc. v. Mylan Laboratories, Inc.*, 520 F.3d 1358 (Fed. Cir. 2008). In *Ortho-McNeil*, the Court found that Ortho-McNeil's compound topiramate was not obvious over known design choices for finding diabetes drugs. In reaching this conclusion, the Federal Circuit stated that Mylan's expert "simply retraced the path of the inventor with hindsight, discounted the number and complexity of the alternatives, and concluded that the invention of topiramate was obvious." *Id.* at 1364. Similarly, the examiner has not recognized the complexity and multitude of options available to Appellants at each or juncture in the process of preparing the dsRNA of the claimed invention.

In *Ortho-McNeil*, the Court stated that one of ordinary skill in the art would have to have some reason to select (among several unpredictable alternatives) the route that would ultimately lead to the claimed invention. 520 F.3d at 1364. The challenges of the inventive process would have prevented one of ordinary skill from traversing the multiple obstacles and arriving at the claimed invention. *Id.* at 1365. In this case, like *Ortho-McNeil*, one of ordinary skill would have to have a rationale for selecting the particular route, amid unpredictable alternatives, that would have lead to the claimed invention. Appellants respectfully submit that such a rationale has not been shown by the examiner.

When confronted with the problem that Appellants faced before this invention, one skilled in the art would glean no useful information from Fosnaugh to assist in solving the recognized problem. Certainty, one skilled in the art would not interpret Fosnaugh as teaching that difficulties associated with conjugating through the 5' end of the antisense strand could be

overcome by its broad, generic disclosures. See Appellants' Response filed February 12, 2010, describing how the prior art disfavors conjugation at the 5' end of the antisense strand, particularly in instances when a free hydroxyl group is not present at the 5' end.

MPEP § 2143.01 states that the fact that references can be combined or modified does not render the resultant combination obvious unless the results would have been predictable to one of ordinary skill in the art. This is especially pertinent to the case at hand in view of the numerous reports disfavoring modifications at the 5' end of the antisense strand. The same section of the MPEP states that the mere statement that the claimed invention is within the capabilities of one of ordinary skill in the art is not sufficient by itself to establish *prima facie* obviousness.

Rejections of obviousness cannot be sustained by mere conclusory statements such as that offered by the examiner in the November 12, 2009 Office Action; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness. This is especially true in cases involving new chemical compounds, where it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish *prima facie* obviousness. See *Takeda Chemical Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1357 (Fed. Cir. 2007).

Motivation to Combine

The examiner contends that the motivation for attaching a lipophilic group to the 5' end of the antisense strand of a dsRNA is provided by Manoharan, Mackellar and Virta. See pages 4-7 of the Office Action mailed January 18, 2011. Manoharan is cited by the examiner as disclosing that conjugation of cholesterol to the 5' end of an antisense molecule presents better serum stability and is more efficient at reducing target gene expression *in vivo*. See Office Action mailed July 30, 2010, pages 9-10. Mackeller allegedly discloses that the benefits of attaching a cholesterol moiety to the 5' end of an oligonucleotide were well known in the art. See Office Action mailed July 30, 2010, page 9. Virta is also cited as teaching that attaching conjugates to the 5' end is a simpler process than the 3' end. See Office Action mailed July 30, 2010, pages 9-11.

Despite the examiner adding three additional references to this rejection, Applicants respectfully submit that none of the references provide one skilled in the art with the requisite

motivation to conjugate a lipophilic group to the 5' end of the antisense strand of a dsRNA through a phosphodiester linkage.

With respect to the examiner's assertion in Manoharan that "the 5' cholesterol conjugated oligonucleotide was more effective at reducing target gene expression *in vivo*," the full passage clearly shows that the better efficacy was based on the comparison between the 5' end conjugated and the unconjugated oligonucleotide, not the comparison between the 5' end conjugated and the 3' end conjugated oligonucleotide. Thus this citation from Manoharan cannot be used as a motivation for one skilled in the art to attach conjugates to the 5' end rather than the 3' end.

The examiner also cites a passage in Manoharan stating that the authors "found the 5' cholesterol conjugated … had a plasma half life … greater than the 3' cholesterol conjugated oligonucleotide." However, this too is not supported by a full reading of Manoharan. See pages 107-109 of Manoharan, in particularly, the example on page 107, left column and the example on page 109, left column. The first example shows that a 3'-end cholesterol conjugation to an antisense was more active than the 5' end (page 107, left column); and the second example demonstrates that the 5'- cholesterol conjugated oligonucleotide did not present enhanced resistance to metabolism as compared to the unconjugated oligonucleotide, while the 3' cholesterol conjugated oligonucleotide was more stable than the 5' end conjugated and the unconjugated oligonucleotide (page 109, left column). Therefore, a complete reading of Manoharan suggests that, contrary to the examiner's assertions, the 5' end conjugation is not more stable and more active than the 3' end conjugation for an antisense oligonucleotide. Hence Manoharan cannot be relied upon as providing the motivation to attach a lipophilic group to the 5' end of the antisense rather than the 3' end through a phosphodiester, or otherwise cure the deficiencies of Kay and Fosnaugh, identified above.

With respect to Mackeller, the examiner alleges that "the benefits of attaching a cholesterol moiety to the 5' end of an oligonucleotide were well known in the art." See Office Action mailed July 30, 2010, page 9. However, Mackeller merely discloses that a lipophilic group can be covalently attached to either the 5' or the 3' termini of oligonuceotides. See Mackeller, "Conclusion" on page 3413. Mackeller provides no guidance regarding whether the lipophilic group should be attached to the 5' end or the 3' end. Further, Mackeller fails to teach

or suggest the lipophilic conjugation method to an antisense strand in <u>a dsRNA agent</u>. Similarly, Virta, directed to a general synthetic strategy of oligonucleotide conjugation, also fails to teach or suggest the lipophilic conjugation method to an antisense strand in a dsRNA agent. Mackellar and Virta together disclose nothing more than the general synthetic strategy of conjugation to an oligonucleotide. Accordingly, Mackellar and Virta, like Manoharan, fail to provide one skilled in the art with the requisite motivation to conjugate at the 5' end of the antisense rather than the 3' end through a phosphodiester, or otherwise cure the deficiencies of Kay and Fosnaugh, identified above.

Applicants clearly point out in the specification that "<u>[D]espite efforts in increasing the efficiency of antisense technology</u>, particularly by enhancing uptake of antisense oligonucleotides by cells, <u>there is currently no known means for improving the efficiency of RNA interference by dsRNA</u>. Thus, there remains a need for a more effective dsRNA molecule that can selectively and efficiently silence a target gene... ." Just because Manoharan teaches a conjugation method to an antisense oligonucleotide in an antisense technology does not mean the same technology would be applicable for a dsRNA to show stability and gene silencing activity. Likewise, just because Mackellar and Virta teach the synthetic strategy of conjugation to an oligonucleotide or an antisense does not mean the same strategy could be used to conjugate an antisense strand in the dsRNA, much less conjugate to a dsRNA in a manner that would have made the oligonucleotide stable and possess gene silencing activity.

Even in view of the additional teachings provided by Manoharan, Mackellar and Virta, Appellants respectfully submit that the examiner has not provided the detailed reasoning for why one skilled in the art would choose to conjugate this particular lipophilic compound (a) at the 5' end of the antisense strand, and (b) through a phosphodiester linkage. The problems associated with conjugating at the 5' end of the antisense strand--problems that have been well documented by Appellants--need to be keenly observed in making this analysis. One skilled in the art, knowing all the problems and difficulties in making this type of conjugation would be much less likely to try it. This is not the case where a reference recognizes the problem and teaches specific ways to overcome it. Fosnaugh is completely silent on this art-recognized problem; the 5' end of the antisense strand was simply provided as part of a comprehensive disclosure

suggesting that Fosnaugh's particular conjugate could be attached through any means possible. The deficiencies of Kay and Fosnaugh, described above, have not been overcome by the additional teachings of Manoharan, Mackellar and Virta.

Expectation of success

At the time of the invention, those of ordinary skill in the art understood that there were clear differences for conjugation strategies in general synthesis of oligonucleotide, antisense technology and dsRNA technology; and that there were clearly different structural features of nucleic acids required for activity in each, for example, dsRNA, antisense and aptamer technologies, because the mechanism of action of these nucleic acids differed in each. At the time of the invention, the mechanism of dsRNA had not yet been explored to the extent that one of ordinary skill in the art understood or could predict the effect of a conjugation in a strand on gene silencing activity of the dsRNA.

Moreover, <u>irrespective the teachings in the antisense technology,</u> at the time of the invention, the art of RNA interference as a whole would have steered one skilled in the art away from proceeding in the manner chosen by Applicants. Based on the art of RNA interference at the time of the invention, one skilled in the art would have expected that a dsRNA with 5' end modifications in the antisense strand, regardless the type of the conjugates, is unable to cause RNA interference.

As disclosed in the specification and discussed in previous responses, various references have shown that the 5' end phosphodiester modification of an antisense strand of a dsRNA completely abolished, or at least reduced, its activity compared to a dsRNA with an unmodified antisense strand, largely because blocking the 5'-OH of the antisense strand inhibited the ability of a siRNA to interfere with the expression of its target gene. As known to one skilled in the art of RNA interference at the time of the invention, the 5'-OH of the antisense strand of an siRNA was believed to be important and necessary for RNAi activity, because *in vivo* kinase was considered a required process for RNAi activity; an antisense strand, if the 5'-OH is blocked, cannot be further phosphorylated by kinase *in vivo*. Thus, taking together all teachings in the art of RNA interference, one skilled in the art would not have been motivated to modify the 5'-OH of the antisense strand with the expectation that the dsRNA could enable RNAi interference. See

pages 2-3 of the specification and pages 6-7 of the Response filed February 12, 2010. One skilled in the art would not ignore the clear teachings of these references and attempt conjugation of a phosphodiester linker through the 5' end of the antisense strand of the dsRNA with any expectation of success.

Indeed, in view of the art as a whole, one would have no reasonable expectation of successfully preparing the claimed invention in view of the art-recognized failures in this area. In fact, it was not until this invention that the inventors recognized that a highly lipophilic group can be conjugated on the 5' end of the antisense strand of a dsRNA through the use of a phosphodiester linkage while still maintaining or even improving the biological activity and RNA interference activity of the dsRNA.

Unexpected results

None of the references suggest the benefits Appellants have discovered associated with using lipophilic compounds having high $\log K_{ow}$ values. Using groups having increased lipophilic properties that are covalently linked to the dsRNA has enabled the dsRNA to exhibit increased uptake by cells with or without a transfection aid. The derivatized dsRNA show surprisingly improved activity regardless of the mechanism of entry into the cell. Unlike similarly conjugated antisense RNA, the improved activity of the dsRNA of the claimed invention is independent of cellular association or receptor binding, and thus not a consequence of enhanced transport across cell membranes. See specification, page 17, lines 14-23.

Because of the highly lipophilic nature of these groups, Appellants have found that the dsRNA may be used "exclusively"; i.e. without auxiliary agents or encapsulating substances that might affect or mediate uptake of dsRNA in the cells that harbor the virus. Surprisingly, the inventors have discovered that compositions containing only naked dsRNA and physiologically acceptable solvent are taken up by cells, where the dsRNA effectively inhibits replication of the virus. The dsRNA of the claimed invention are thus particularly advantageous in that they do not require the use of an auxiliary agent to mediate uptake of the dsRNA into the cell, many of which agents are toxic or associated with deleterious side effects. See specification, page 22, line 18 to page 23, line 7.

In the Office Action mailed July 30, 2010, the examiner responds to Applicants' arguments relating to the unexpected results, stating that the results are what have been shown in the prior art and what is expected when conjugating a cholesterol group to the 5' end of an oligonucleotide. See Office Action mailed July 30, 2010, page 14.

Applicants respectfully disagree with the examiner's assertion. As Applicants have discussed above, one skilled in the art would not have expected, before this invention, that dsRNA with 5' end modifications in the antisense strand would cause RNA interference. Yet despite this, Applicants have surprisingly discovered that covalently linking a highly lipophilic group through a phosphodiester linker to the 5' end of the antisense strand of a dsRNA <u>is actually stable and maintains or even improves the RNA interference activity and the biological activity of the dsRNA</u> compared to the unconjugated control. See specification, pages 32-33 and Fig. 3.

In Fig. 3, Applicants provide various compounds conjugated with highly lipophilic groups. Four of these compounds, HCVC32-as, GalC32-as, HCVChol-as, and GalChol-as, illustrate examples of lipophilic groups covalently attached to a 5' end of the antisense strand of a dsRNA through a phosphodiester linker. See pages 32-33 of the specification. The lipophilic group cholesteryl (6-hyroxyhexyl) carbamate ("Chol") and 12-hydroxydodecanoic acid bisdecylamide ("C32") are specifically recited in claim 97. Fig. 3 demonstrates that dsRNA of the claimed invention, i.e. having one lipophilic group having a $\log K_{ow}$ exceeding one where the lipophilic group is covalently attached to the 5' end of the antisense strand and where the RNA strand contains a phosphodiester group, achieve an approximate 10-20% reduction in gene expression. Applicants use these results as examples to demonstrate the unexpected advantages exhibited by the claimed dsRNA having an antisense strand covalently linked to lipophilic groups through a phosphodiester linker.

The examiner also acknowledges that "Figure 3 does in fact show a dsRNA of the claimed invention having a cholesterol attached at the 5' end [of an antisense strand] and shows what appears to be a reduction of expression of a B-gal gene up to 20% as compared to the [unconjugated] control." However, the examiner contends that the same conjugation at the 3' end showed an even greater reduction in gene expression as compared to the control and thus the results are not unexpected because "the evidence does not support the arguments that

conjugation of cholesterol at the 5' end allows the dsRNA to have increased uptake and unexpected results as compared to a dsRNA molecule with a conjugate at the 3' end." See Office Action mailed July 30, 2010, page 14.

Applicants respectfully disagree with the examiner's conclusion. As shown in the specification as well as in various references in the art at the time of the invention, the 5' end phosphodiester modification of an antisense strand of a dsRNA of a lipophilic group completely abolished, or at least reduced, its activity compared to an unmodified antisense strand, because blocking the 5'-OH of the antisense strand inhibited the ability of a siRNA to interfere with the expression of its target gene. See pages 2-3 of the specification and pages 6-7 of the Response filed February 12, 2010. Therefore, what is unexpected and surprising is that conjugation of a lipophilic group to the 5' end of an antisense strand through a phosphodiester modification of a dsRNA would actually enable or even improve the RNA interference activity and the biological activity of the dsRNA. This discovery itself is surprising and unexpected in view of what has been presented in the relevant prior art references.

These advantages discovered by Appellants provide an example of the unexpected results exhibited by the claimed dsRNA covalently linked to highly lipophilic groups. Additionally, these advantages demonstrate the benefits associated with the lipophilic groups, in particular with regard to lipophilic groups having a $\log K_{ow}$ exceeding 1.0, and certainly for lipophilic groups having a $\log K_{ow}$ exceeding 1.5.

None of the references applied by the examiner disclose the benefits and surprising results discovered by Appellants associated with the lipophilic groups. The examiner must consider these unexpected results in determining obviousness. See MPEP § 716.02(c) ("Evidence of unexpected results must be weighed against evidence supporting *prima facie* obviousness of the claimed invention.").

Additional References cited by the Examiner

To make this obviousness rejection, the examiner has deemed it necessary to combine the teachings of five prior art references. While the examiner has the difficult task of combining just these five references—the examiner carries the burden of showing that one skilled in the art would select particular teachings from each of these references and combine those teachings in a

way to arrive at Applicants' claimed invention—the examiner has cited two additional references in last Office Action. Pages 7-9 of the January 18, 2011 Office Action cite Rana and Schwarz, references that the examiner previous applied to the claims, but then later withdrew.

Applicants respectfully submit that if the examiner is going to rely on the teachings of a reference, that reference must be set forth in the rejection. The examiner must then show the rationale for why one skilled in the art would combine the teachings of the two new references with the other five references. Rana and Schwarz were withdrawn by the examiner because the examiner could not make this showing. The examiner cannot, at this point in the prosecution, rely on the teachings of those references without making them part of the rejection.

In view of the foregoing, it is clear that the rejections of the pending claims under 35 U.S.C. § 103(a) cannot be sustained. Accordingly, Appellants respectfully request that the Board reverse the rejection of claims 86, 94-98, 100-102, 110-111, and 114-119.

Respectfully submitted,

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VIII. CLAIMS APPENDIX

86. A double-stranded ribonucleic acid (dsRNA) comprising a complementary RNA strand, a sense RNA strand and only one lipophilic group having a $\log K_{ow}$ exceeding 1, wherein the complementary RNA strand has a nucleotide sequence which is complementary to a target RNA, and wherein the target RNA is an mRNA transcript of a target gene or of a (+) strand RNA virus, wherein the lipophilic group is covalently attached to a 5'-end of the complementary RNA strand and a linkage between the lipophilic group and the 5'-end of the complementary RNA strand comprises a phosphodiester group.

94. The dsRNA of claim 86, wherein the lipophilic group is a steroid or a branched aliphatic hydrocarbon, or a combination thereof.

95. The dsRNA of claim 94, wherein the lipophilic group is a sterol.

96. The dsRNA of claim 95, wherein the sterol is cholesterol or a cholesterol derivative.

97. The dsRNA of claim 96, wherein the lipophilic group is cholesteryl (6-hydroxyhexyl) carbamate or 12-hydroxydodecanoic acid bisdecylamide.

98. The dsRNA of claim 86, wherein the lipophilic group is selected from the group consisting of an aromatic, aliphatic or alicyclic moiety, or a combination thereof.

100. The dsRNA of claim 86, wherein the lipophilic group has a $\log K_{ow}$ exceeding 1.5.

101. The dsRNA of claim 86, wherein the lipophilic group has a logKow exceeding 2.

102. The dsRNA of claim 86, wherein the lipophilic group has a logKow exceeding 3.

110. The dsRNA of claim 86, wherein the complementary RNA strand comprises a 3'-end and a 5'-end, and wherein the 3'-end has a nucleotide overhang of 1 to 4 nucleotides.

111. The dsRNA of claim 86, wherein the complementary RNA strand comprises a 3'-end and a 5'-end, and wherein the 3'-end has a nucleotide overhang of 1 or 2 nucleotides.

114. The dsRNA of claim 86, wherein the dsRNA is between 16 and 30 nucleotides in length.

115. The dsRNA of claim 86, wherein the dsRNA is between 16 and 25 nucleotides in length.

116. The dsRNA of claim 86, wherein the dsRNA is between 20 and 25 nucleotides in length.

117. The dsRNA of claim 86, wherein the target RNA is expressed in a cell selected from the group consisting of a hepatocyte, a pancreatic cell, a uterine cell, a cell of a cervix, and a cell of a urinary bladder.

118. The dsRNA of claim 86, wherein the (+) strand RNA virus is a Hepatitis C Virus (HCV).

119. The dsRNA of claim 86, wherein the target RNA is at least a portion of a 3'-untranslated region (3'-UTR) of a Hepatitis C Virus (HCV).

IX. EVIDENCE APPENDIX

There is no additional evidence being submitted in the Evidence Appendix.

X. RELATED PROCEEDINGS APPENDIX

There are no decisions rendered by a court or the Board on related appeals or interferences.